AMA
AMERICAN MEDICAL ASSOCIATION

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February 15, 2019

The Honorable Frank Pallone, Jr.
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Greg Walden
Ranking Member
Committee on Energy and Commerce
U.S. House of Representatives
2322A Rayburn House Office Building
Washington, DC 20515

The Honorable Diana DeGette
Committee on Energy and Commerce
U.S. House of Representatives
2111 Rayburn House Office Building
Washington, DC 20515

The Honorable Larry Bucshon
Committee on Energy and Commerce
U.S. House of Representatives
2313 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Pallone, Ranking Member Walden, Representative DeGette, and Representative Bucshon:

On behalf of the physician and medical student members of the American Medical Association (AMA), I appreciate the opportunity to provide comments on H.R.__, "Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2018." The AMA is committed to modernizing the oversight of clinical testing, particularly high-complexity proprietary black box next generation genetic and genomic testing. We appreciate that the Committee on Energy and Commerce (Committee) leadership is seeking broad and representative input from clinicians. The AMA looks forward to working with you and regulators to ensure modernization of clinical testing oversight advances patient safety without compromising access and public health readiness and response capabilities, promotes continued world class innovation, and reduces the growing and costly regulatory and reporting burdens. The AMA also urges the Committee to work closely with clinician organizations representing those who deliver care directly to patients and are responsible for the day-to-day realities of patient care and clinical testing.

Clinical Laboratory Improvement Act Amendments (CLIA)

The AMA urges the Committee to consider that the CLIA framework has provided an oversight regime that has supported unprecedented access to safe, affordable, and innovative clinical testing. Since the mapping of the human genome and rapid advances in computing, the nexus between clinical laboratories and the physicians delivering care directly to patients in a growing number of cases has become more attenuated, particularly in the area of genetic and genomic testing. CLIA is a framework that was crafted to provide oversight of community-based and well-established reference laboratories that are part of an integrated continuum of care centered in close proximity to the patient and where the culture drives transparency and participation in sharing clinical findings and discoveries to allow validation by other clinicians (and thereby establishing a shared medical commons). However, in the past decade, there has been a rapid proliferation of stand-alone clinical laboratories, serving communities around the nation, that eschew participation in the medical commons, e.g., laboratories that consistently fail to contribute to the ClinVar registry, a freely accessible, public archive of reports of the relationships among human

variations and phenotypes, with supporting evidence. While some have argued that these clinical laboratories have driven innovation, the AMA notes that innovation has been driven in large part by academic medical systems, established clinical providers, and reference clinical laboratories that are active in contributing to the medical commons. **The AMA urges the Committee to move swiftly to prioritize oversight of clinical laboratories that (1) seek to serve large markets outside of the community where testing is performed; (2) offer proprietary, black box clinical tests typically with significant bioinformatics; and (3) do not contribute to advancing the medical commons by, among other things, providing transparent evidence of clinical validation nor demonstrate adherence to accepted standards (including evidentiary).**

The foregoing prioritization would ensure that laboratories (like Theranos[1]) that eschew transparency and participation in the medical commons and that lack ongoing responsibility for patient care receive the oversight required to protect against patient harm. **The AMA also supports regulatory updates under CLIA targeted to support oversight modernization applicable to all clinical testing put forward by national medical specialty societies, such as the College of American Pathologists.** The latter can result in successful modernization where there are limited resources available to regulators and providers.

Practice of Medicine

The AMA supports the inclusion of a provision in the draft legislation that explicitly specifies that the U.S. Food and Drug Administration (FDA) does not have authority to regulate the practice of medicine. We appreciate that this provision specifies that Congress does not intend to confer the FDA with new authorities that would negatively impact patient care and undermine the ability of physicians to meet the specific needs of their patients through medical practice.

Costs and Regulatory Burdens

We urge the Committee to consider that the modernization of clinical laboratory testing oversight should be done in the context of the challenges currently faced by providers of clinical testing resulting from the Protecting Access to Medicare Act of 2014 (PAMA). The PAMA cuts to Medicare payment for clinical testing were substantially larger than original Congressional Budget Office projections, and there are reports that smaller independent community providers are now struggling under the payment cuts. We urge careful consideration and analysis of the cost burden associated with the VALID Act modernization framework coupled with the continuing cuts into the foreseeable future due to PAMA's payment methodology.

Furthermore, we are concerned that the draft legislation does not outline the least burdensome approach to modernization. As a result, this proposed legislation could negatively impact access in underserved communities and over time, perversely, result in the escalation of prices as the current competitive market

[1] For example, Theranos advertised breakthrough technologies, but was not able or willing to subject the new testing methods and systems to rigorous peer review of other scientists and clinicians. Reportedly, Theranos also changed the company's business model to skirt FDA regulation even though their intention was to operate nationally.

for clinical testing services becomes less competitive, with only a few of the largest laboratories able to survive the severe PAMA payment cuts.

We urge the Committee to require the Centers for Medicare & Medicaid Services (CMS), in coordination with the FDA and the Centers for Disease Control and Prevention (CDC), to implement a fact-gathering and modernization effort that is similar to the one under way at the FDA involving software as a medical device (SaMD). The FDA has been evaluating a streamlined, CLIA-like approach to oversight of SaMD called the Pre-Certification Program (Pre-Cert). In order to develop the Pre-Cert Program, the FDA has interviewed and gathered information from nine companies[2] for over a year to develop a voluntary, streamlined pathway for SaMD oversight. The FDA recently launched a pilot to test the Pre-Cert framework for 2019. Thus, the FDA's approach to developing the Pre-Cert Program is an example of giving consideration to the factors that support innovation and safety as well as the least burdensome approach to regulation.

VALID Act

The AMA agrees that targeted modernization is needed and that the FDA requires new authority to provide adequate oversight to clinical laboratories that have similar profiles to Theranos. The AMA has advocated for such targeted FDA authorities previously. (See enclosed comments.) We urge the Committee to consider these comments.

We are concerned that the scope of the VALID Act as currently drafted will decrease patient access, have a deleterious impact on patient health outcomes, and over time lead to laboratory consolidation that will harm innovation and raise costs. The following are examples of how the current draft of the VALID Act provisions could, broadly applied, create significant concerns:

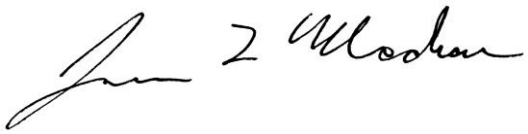
- **Duplicate Fees**. The draft bill would impose user fees on clinical laboratories even though they already are required to pay CLIA user fees. In contrast, manufacturers of mass-distributed-and-produced commercial test kits would only have one set of fees.
- **Duplicate Notification**. The draft bill would impose duplicate requirements for test notification to the FDA and to CMS, the latter of which is responsible for CLIA compliance.
- **Limited Value of Grandfathering.** Although the legislation provides for grandfathering of certain existing clinical tests, this provision is negated where modifications are made. The reason the grandfathering provision is needed is because the FDA lacks the resources and expertise to provide the oversight outlined in the draft bill for all clinical tests today and well into the foreseeable future. Furthermore, clinical laboratories are not able to meet the duplicative regulatory demands under both CLIA and new FDA requirements. This reform model does not target the FDA's resources to the highest risk tests.

[2] Note that the Software Pre-Cert Program did not include any providers of laboratory developed testing services and procedures, and it may not be possible for example to extrapolate these experiences, such as those of Roche, to clinical laboratories.

- **Exempt Categories.** The draft bill does not account for the realities of clinical practice or public health exigencies. For example, the rare disease exemption is not adequate and should be based on the incidence of the disease. The bill also does not include the flexibilities needed to address emerging and infectious disease outbreaks and associated need for rapid diagnostics. We urge the Committee to consult with national medical specialty societies to obtain more detailed feedback on how patients with rare diseases would be impacted under this legislation as well as the negative impact on public health readiness and response capabilities.
- **Definition of High-Risk.** The high-risk definition in the draft bill is very broad and can include many varied situations, including cross-referenced tests (which may not be authorized by the developer) and first-of-a-kind tests which may otherwise be low-risk. The risk classification should be straightforward. The high-risk definition should be narrower in scope, and mostly limited to clinical testing whose accuracy cannot be independently verified. We urge the Committee to specify that high risk tests are those that lack transparency, such as proprietary black box algorithms using bioinformatics and are marketed nationally. We also support restrictions authorized for tests without input from health care professional, such as direct-to-consumer tests as listed in the draft legislation.

We appreciate the opportunity to address these issues with the Committee and would welcome further discussion to ensure that modernization efforts prioritize the highest risk clinical testing, minimize regulatory duplication, and advance the tremendous innovation that is transforming medical care.

Sincerely,



James L. Madara, MD

Enclosure

STATEMENT

of the

American Medical Association

for the Record

U.S. House of Representatives
Committee on Energy and Commerce
Subcommittee on Health

Re: 21st Century Cures—Request for Feedback:
A Modernized Framework for Innovative Diagnostic Tests

January 5, 2015

The American Medical Association (AMA) appreciates the U.S. House of Representatives Committee on Energy and Commerce Subcommittee on Health's (Subcommittee) efforts to build on and accelerate wide-spread clinical applications of innovative tests. We welcome the opportunity to respond to the questions posed by the Subcommittee. Our responses are below along with examples that demonstrate the differences between medical testing services offered by physicians in a single laboratory to address a specific patient medical need versus the packaged commercial products that are shipped by manufacturers to laboratories across the country. The AMA strongly supports both legislative reform of (1) the current oversight of laboratories where testing services are offered by physicians; and (2) the Food and Drug Administration's (FDA or Agency) regulation of mass-produced commercial test kits. Congressional action is needed in order to sustain and encourage widespread access to well-established tests while removing burdensome regulatory barriers to rapid adoption of innovative tests that are clinically indicated.

In the interest of safeguarding patient access to existing standard-of-care testing services and the innovation that has inspired development and provision of new cutting-edge tests, it is critical that the Subcommittee move quickly to advance legislation that:

- **Rescinds FDA Proposed Guidance:** Directs the FDA to rescind the Agency's proposed guidance to regulate laboratory developed testing services and clarifies that the Agency is prohibited from regulating physicians engaged in the practice of medicine including the procedures and analysis that physicians perform in clinical laboratories;
- **Modernizes CLIA:** Modernizes the Clinical Laboratory Improvement Amendments (CLIA) to, among other things, strengthen the role of third party accreditors;
- **Reforms FDA Oversight of Commercial Kits:** Reforms current FDA regulation of commercial diagnostic kits distributed by manufacturers in order to address the extensive and well-documented concerns of manufacturers that the current FDA regulation is costly, overreaching, and so slow that some commercial kits become obsolete before they reach the market;
- **Provides Limited FDA Oversight of Black Box Testing:** Confers limited authority on the FDA to regulate direct to consumer tests and testing services where incorrect results could cause harm to

patients and the test methodology is **not transparent nor well understood** (as in the case of tests that use black box complex algorithms to produce results).

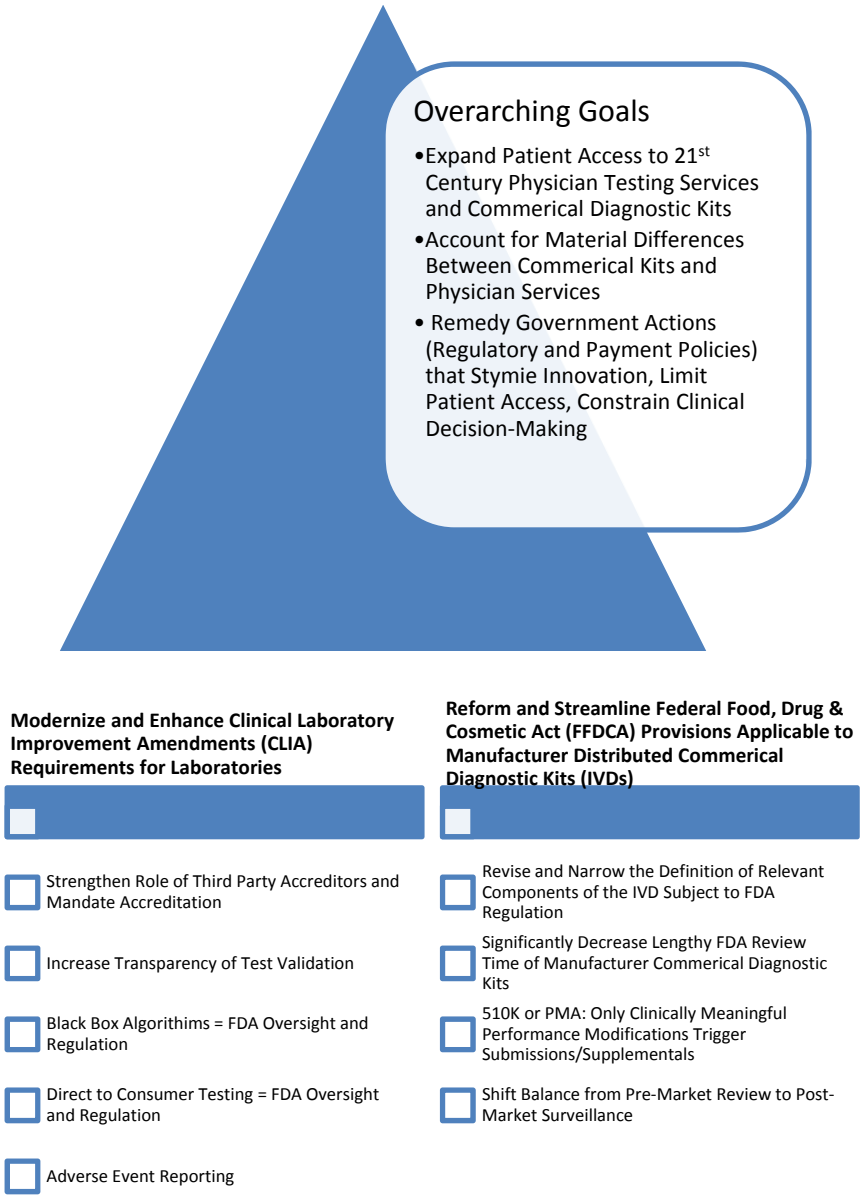


Figure 1. Changes to CLIA and the FFDCA are needed to promote patient access to effective tests, account for differences between commercial kits and physician services, and remedy government actions that harm innovation, limit patient access, and hamper clinical decision-making.

Context: FDA's Current and Proposed Regulation Jeopardizes Access to Established Testing Services that Will Negatively Impact Patient Clinical Care

Physicians have been and continue to be at the forefront of the intersection of providing patients' medical care and advancing medical knowledge to improve upon the current standard of care. Physicians are unique stakeholders who have both an ethical and legal obligation to each individual patient to whom they

render medical care. The first directive of physicians is to do no harm and to advance the interest of their patients to whom they provide medical services. While there are important interested stakeholders focused on commercializing innovations and regulators tasked broadly with safety, physicians have a direct relationship with patients and an obligation to provide medical services that meet patient specific clinical needs; these are services physicians have provided for decades in the context of laboratory developed testing services.

The AMA is very concerned that patient access to **well-established, standard-of-care** testing services provided by physicians to millions of patients each year will no longer be available once the FDA finalizes the Agency's proposed regulation of laboratory developed testing services. Though there are many unanswered questions raised by the FDA's proposal, it is already clear that the proposed guidance would impose new, costly, and burdensome requirements on even low- and moderate-complexity testing services. More troubling, the Agency has repeatedly acknowledged it does not know the number of times these testing services are offered or the universe of services being offered by physicians that would be subject to this regulation while at the same time claiming that adequate Agency capacity exists to regulate such physician services. Many of these testing services, along with those that potentially will be categorized as high-risk by the Agency, have represented the standard-of-care for years.

As a threshold matter, the FDA has offered little to no evidence that patients have suffered harm on a persistent or widespread basis justifying the imposition of broad new and costly regulatory requirements that will harm patients who are unable to obtain needed testing services. When queried as to what problem the FDA is addressing and any corresponding documented patient harm, the Agency has declined to identify the number of testing services and patients that the FDA has identified or tracked or scoured from literature or media accounts. We have urged the FDA to define and identify the problem(s) and the breadth thereof before proceeding with any plan to implement oversight. The FDA appears to have conflated one problem—lack of incentives to seek FDA approval/clearance—with a poorly articulated statement of patient harm vis-à-vis laboratory developed testing services.

To the extent that the Subcommittee and others are interested in developing new incentives to accelerate the commercialization of mass-produced testing kits—particularly genetic or next generation commercial kits, we strongly urge reform to the FDA's current regulation of mass-produced testing kits. We further support CLIA modernization to enhance the oversight of laboratories where physician services are offered through increased transparency as opposed to the expansion of the flawed FDA commercial kit regulation framework to physician services.

The FDA's proposed regulation of laboratory developed testing services will have a sweeping and widespread negative impact on patient access to established testing services representing the standard-of-care. The proposed regulation will leave the country vulnerable to biothreats and outbreaks of infectious diseases. Why? Because the Agency's action will lead to a reduction in the number of testing services that physicians are able to offer and the laboratories where these services are performed. The FDA's actions will create strong disincentives to maintenance of laboratory resources needed to offer new laboratory testing services because of the potentially short duration of time in which the tests could be offered and, over time, there will be fewer physicians with the training and expertise to offer these services. The Agency's proposed regulation will markedly dampen the ground-breaking innovations developed by physicians as part of their laboratory clinical practice of medicine—innovation that is the genesis of commercial tests kits and a key part of a physician's ability to properly diagnose and treat patients. At the same time that the FDA's regulation will erect additional impediments to medical advancement in the U.S., it will contribute to increased costs associated with (1) poor patient outcomes given decreased access, and (2) increases in per test costs because of limited competition.

Finally, if the FDA's concern is primarily related to highly complex genetic/genomic tests, the proposed ten year window for phasing-in FDA's regulation of all laboratory developed testing services (including a large number that are not genetic or genomic tests) will divert limited Agency and health care system resources away from developing a workable regulatory framework to address the manufacturing challenges associated with next generation and whole genome sequencing and associated testing. The technical and clinical expertise that will be required to develop such a framework, implement the framework, and monitor compliance will be significant. The FDA's approach—creating a highly complex regulatory and rigid framework when the field is undergoing seismic changes that will bring ground breaking testing and treatment advances—is at odds with this Subcommittee's goal of promoting 21st Century Cures.

Subcommittee Questions & AMA Answers

Answer to Question #1: Practice of Medicine v. Commercial Kit

1. Multiple stakeholders have expressed the urgent need to have clear and logical lines separating the practice of medicine, the actual conduct of a diagnostic test, and the development and manufacturing of diagnostic tests. How should these lines be defined and what are the key criteria separating each of these activities?

The AMA would like to underscore the differences between the practice of medicine (which laboratory developed testing services are) and mass produced commercial kits that are shipped by manufacturers around the country. Laboratory developed testing services are procedures performed by physicians for specific patients equivalent to a surgeon who provides surgical services to a specific patient. A physician practicing laboratory medicine will utilize reagents (products that are subject to FDA regulation) and machines (which may or may not be FDA regulated) when conducting testing, but the laboratory testing services are the technical expertise and clinical judgment of a physician who develops and validates the test performed under testing conditions that are already subject to oversight under CLIA. The physician makes a clinical determination as to what products to utilize, what patient sample preparation is needed, and what machines are used in order to perform the testing services. A physician who develops, validates, and performs the testing procedures is knowledgeable about each component part and each step and procedures involved with the test. The physician's services cannot be packaged and shipped to multiple laboratories.

Critical distinctions exist between laboratory developed testing services and commercial diagnostic kits	Commercial diagnostic kits are an actual product that can be packaged, labeled, and **shipped in interstate commerce to numerous laboratories**, in contrast to the services and procedures offered by a physician in **a single laboratory as part of his or her practice of medicine**.
	Once the manufacturer distributes the commercial diagnostic kits, the **manufacturer no longer retains contro**l over how the test is conducted, what patient is tested, and how the information is shared with the treating physician, whereas **physicians retain control and decision-making authority** throughout the continuum from design to delivery of test results.
	Physicians who utilize a **commercial diagnostic kit are not able to evaluate the underlying methods and components of the commercial kit**, **nor are the test results detailed**; instead, they are limited to yes/no results. In contrast, when offering laboratory developed testing services **physicians have a complete understanding** of the results as well as the underlying methods, sample preparation, inputs, procedures, and validation of the test.
	A commercial diagnostic kit is a packaged product that is **engineered** to be performed **anywhere** for a **"standard" patient**, not a specific patient in contrast to **laboratory developed testing services that physicians offer to a specific patient** based on their clinical condition and in consultation with the patient's treating physician.

Simply stated, laboratory developed testing services are analogous to a unique home built by a master craftsman to meet the specifications of the homeowner, and manufactured commercial diagnostic kits are standard tract housing built with prescribed specifications and products with no consideration of the preferences of the homeowner or the conditions under which the house is to be built.

Oversight and responsibility for design, development, validation, monitoring, and reporting attendant to laboratory developed testing services constitute the practice of medicine. These are within the scope of a physician's practice and physicians have a legal responsibility for them. In contrast, with commercial diagnostic kits the design, development and manufacturing is physically and distinctly separate from the laboratory operations, including sign-out of tests (meaning the reporting, record review, and other components of communication with treating physician colleagues). With laboratory developed testing services, the physician practice components of design, development, monitoring, and application to clinical care are inseparable and inextricably linked.

In order to offer these medical services to patients, physicians practicing laboratory medicine have completed post-graduate medical training and, taken board-certification examinations administered by the American Board of Pathology or the American Board of Medical Genetics and Genomics under the umbrella of the Accreditation Council for Graduate Medical Education. Physicians continue to maintain certification under the American Board of Medical Specialties, are licensed by state medical boards, and pay for and are covered by medical malpractice insurance.

Real Life Implications for Patients

Dr. X consulted me (a physician laboratory director) about a patient taking clopidogrel and testing for CYP2C19. I explained that while there is both the FDA-cleared assay and the laboratory-developed procedure and that they are analytically equivalent (report the same genotype), the difference between the two assays is the interpretation for CYP2C19 heterozygotes. The FDA-cleared assay reports all heterozygotes as extensive or normal metabolizers. This suggests that a normal dose of clopidogrel can be given to the patient. The laboratory developed procedure, in accordance with the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, reports heterozygotes as intermediate metabolizers. CPIC recommends an alternative antiplatelet therapy (if no contraindication), e.g., prasugrel or ticagrelor, be given to heterozygotes. I also explained that we could not change the interpretation of the FDA-cleared assay.

After obtaining my medical degree and completing a residency in medical genetics, I trained for an additional two years and obtained board certification in clinical molecular genetics from the American Board of Medical Genetics and Genomics. I have almost 20 years' experience as a practicing geneticist developing and offering clinical laboratory testing services. On average in my previous laboratory, my team conducted and reviewed approximately 2,000 tests a day. I actively maintain my certification by reviewing literature, writing papers, attending seminars and conferences as a part of my professional development. I understand that some are pushing the FDA to regulate individuals like myself as manufacturers when rendering clinical decisions. This is nonsensical. Laboratory service is part of the practice of medicine. Where professional judgment is used to diagnose and determine a treatment course for a patient, I work in concert with healthcare professionals to determine the appropriate method and test. I am not a "robot" that automatically sends a result regardless of whether the testing is appropriate or not. I continually try to improve my tests and their performance through analytical validation and clinical evidence. Patients are at the center of everything that I do.

Combined Answer to Question #2 and #7: FFDCA Does Not Apply to Practice of Medicine

2. In FDA's draft regulatory framework, the agency describes the extent to which it proposes to regulate LDTs as medical devices under the Federal Food, Drug, and Cosmetic Act (FFDCA). It is relatively clear with respect to distributed test kits what constitutes a "device," but less clear when considering a test developed and performed in a laboratory. What should comprise the "device" subject to regulation by the FDA?

7. We have heard a lot about the practice of medicine and its relationship with medical product "labeling." What should comprise "labeling" for diagnostic tests? Should different standards for dissemination of scientific information apply to diagnostic tests versus traditional medical devices? What about for laboratories that develop, perform, and improve these tests? Should there be regulatory oversight of the information that is provided to the individual patient or health care provider or is that the practice of medicine?

Physician services are not devices and cannot be shoehorned into the FFDCA for purposes of regulating the practice of medicine. This is clearly demonstrated by the device labeling requirements of the statute.

For commercial diagnostic kits, the components of the kit are unambiguously medical devices subject to regulation and the engineered copies of the test kit *in toto* also are a product.

Demonstrating the incongruity of the FDA's proposal, the Agency did not specify in the draft guidance what should be labeled in the context of laboratory developed testing services even though this is an essential element of compliance under the FFDCA. The following is but one example of the Agency's statutory overreach in proposing to regulate physician procedures and clinical decision-making. The FFDCA section 201(k) provides:

> (k) The term "label" means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.
>
> (l) The term "immediate container" does not include package liners.
>
> (m) The term "labeling" means all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.

It is unclear why the FDA did not specify in its proposal what should be labeled in the context of laboratory developed testing services unless it is the intent of the Agency to be the federal regulator of physician medical practice. There are no packaged containers of laboratory developed testing services and the Agency's effort to create a "package" to be labeled would be an obvious legal fiction.

Furthermore, even to the extent that the FDA proposes to define laboratory developed testing services as something other than what they are—physician expertise and procedures—the Agency's application of these provisions to physicians would create liability for off-label use and "promotion" for physicians. Currently, when physicians determine that a product labeled for a specific intended purpose has an alternative beneficial clinical use physicians are permitted to use the product for an "off-label" purpose and are permitted to discuss such use with other physicians. Although there remains an ongoing legal dispute between the FDA and drug, biological, and device manufacturers, manufacturers are generally prohibited from promoting off-label uses and face significant sanctions if and when the Agency can establish that the manufacturer has "misbranded" the product.

Physicians in contrast are able to inform patients and other physicians when a commercial diagnostic kit, labeled for one purpose, has a clinical benefit for another purpose. This is the very definition of medicine, i.e., a physician using his or her clinical expertise to appropriately diagnose and treat a patient who may require care that is not "one-size fits all." Competent and quality medical care rests on physicians' discretion and responsibility to treat patients in a manner that meets each patient's individual needs. Removing a physician's ability to practice medicine off-label will jeopardize patient access to medically necessary, and potentially lifesaving, treatment.

Real Life Implications for Patients

> An oncologist at my medical center requested that our laboratory, directed by myself, a board-certified molecular pathologist, assess a formalin-fixed paraffin embedded tissue sample from recently-diagnosed papillary thyroid carcinoma. The oncologist was aware that 30-50% of papillary thyroid carcinomas contain the BRAF V600E mutation. Since carcinomas carrying the V600E variant are

responsive to several drugs (venmurafenib, dabrafenib, trametinib), the oncologist wanted to find out whether his patient may be a candidate for one of the drugs. The FDA-approved BRAF V600E test kit is intended only for testing melanoma, not thyroid carcinomas. However, using my expertise as a molecular pathologist, I was able to make a slight modification to the FDA-approved kit so that I could detect the BRAF variant in thyroid carcinoma cells. The patient's thyroid carcinoma tested positive for the presence of the V600E variant, an indication that she was a candidate for drugs targeting BRAF V600E. Her oncologist prescribed dabrafenib, and the growth of her tumor has slowed dramatically.

Use of the FDA-approved BRAF V600E kit on any tissue other than melanoma is considered a modification to the intended use, i.e., an off-label use, making it a laboratory developed testing service. As a physician, I need to use every tool available and appropriate to treat my patients. I would have failed my patient if I had not practiced the best medicine possible by testing her thyroid carcinoma for the presence of the V600E variant. Importantly, if the FDA had required that I obtain its approval to use the FDA-approved BRAF V600E test on a tissue for which it was not approved, my patient would have experienced an unacceptable delay in her care that could have severely affected her chances of survival.

When physicians determine that a test "labeled" for a specified use is appropriate for another use, a physician is permitted to employ off-label uses and permitted to discuss off-label uses with other physicians and patients. In contrast, manufacturers are prohibited from off-label promotion. The Agency would have to create a carve-out for off-label promotion in the context of laboratory developed testing services for physicians since such a prohibition on discussing testing options with patients and treating physicians including off-label uses would prevent physicians from meeting both ethical and legal obligations. Furthermore, not only are physicians permitted to discuss off-label uses of devices, drugs, and biologicals, but this is at the heart of innovation. In the course of providing care to patients, physicians are able to identify emerging previously unknown patterns, symptoms, and outcomes that were not otherwise contemplated when a method, approach to medical care, procedure, device, drug, or biological was initially devised for patient care.

Even assuming the FDA had the capacity to timely process a far larger volume of submissions from both manufacturers as well as physicians and laboratories, the latter do not have the resources needed to prepare a submission for FDA clearance or approval. FDA approval is costly and time-consuming even for large corporations often singularly focused on a very small sliver of the universe of tests patients need daily. If off-label uses (also called clinical practice enhancements) required FDA clearance or approval once one manufacturer commercialized a product, all versions of the test including superior versions would most likely cease given the cost and resource barriers. Even if an application could be submitted, timely processing is already a concern as discussed below.

Answer to Question #3: Risk-based Approach

3. FDA intends its regulation of diagnostics to be risk-based. How should risk be defined? Are the types of risks posed by diagnostic tests different from therapeutic medical devices? Are these risks different with LDTs compared to distributed test kits? Is the traditional medical device classification system appropriate for these products?

The AMA generally agrees with other major stakeholders that risks posed by clinical tests are different from therapeutic medical devices. **The current FDA medical device classification, therefore, is not**

appropriate for clinical tests. A new risk-classification for clinical testing, developed with significant stakeholder input, that balances the relative risks posed by clinical tests with the potential benefit of the information that they provide would be most appropriate. As discussed above, there are differences between physician services and mass produced commercial diagnostic kits shipped all over the country. In short, manufacturers lose control over the commercial kit once the kit is shipped. In sharp contrast, a physician remains responsible for providing testing services from design to finalizing the report and discussing with the treating physician. Given the risk associated with rapid multiplication of potential erroneous testing that accompanies commercial diagnostic kits, the FDA establishes rigid rules for test performance to substitute for professional judgment that is not appropriate or desirable for physician testing services. In addition, the test results for commercial kits are extremely limited with few details on how the results were produced, which increases risk associated with evaluating implications for a specific patient.

The AMA supports risk-based regulation of tests. Risk categorization should be determined by (1) the potential of a misinterpreted result to cause harm to a patient, and (2) by test characteristics, e.g., test methodology that is not transparent or well-understood (as in the case of tests that use complex algorithms to produce results). The AMA is seriously concerned, however, by the *a priori* classification of some test types as "high risk" in the absence of any formal risk classification criteria by the FDA. The Agency has stated that high-risk tests will be subject to pre-market approval requirements within 12 months of the guidance being finalized, and that it will release additional guidance on risk classification criteria once its proposed framework is finalized. But it has failed to clearly define the criteria it will use to determine risk. This leaves physicians uncertain of how to determine whether the tests they offer are high-risk and subject to pre-market review within 12 months, and unable to effectively plan for the additional effort and manpower that would be required for pre-market submission. We believe it is essential that the Agency clearly define risk classification criteria before subjecting physicians and the laboratories where they offer their services to burdensome requirements. Further, we find it puzzling that the FDA has already named certain test classes that will be considered high-risk without stating how risk classification criteria were applied to these tests to place them in the high-risk category.

When taking into account the potential of a misinterpreted result to cause harm to a patient, one must keep in mind number of "checks and balances" that accompany laboratory developed testing services. Every laboratory performing clinical testing is CLIA-certified, assuring laboratory performance standards and test accuracy and reliability. Additionally, those performing high-complexity tests must undergo regular proficiency testing. Even further, almost every clinical laboratory chooses to obtain accreditation by a third-party, such as the College of American Pathologists, which holds laboratories to rigorous quality standards and regular inspections.

Once the laboratory test has been run, it is reviewed and signed by the laboratory director—a physician or laboratory medicine expert who is legally responsible for the result. The ordering physician then receives that result and, often in consultation with the laboratory director, uses his or her expertise to subsequently manage patients. This application of professional expertise – by highly trained experts in laboratory medicine and patient care – is essential in mitigating the risk of harm that could come to a patient through a misinterpreted result. **This professional responsibility is present now, without FDA oversight of laboratory developed testing services, and will continue irrespective of additional oversight.**

The professional responsibility of a laboratory director is to ensure that a test run in his or her laboratory produces accurate and reliable results. This often means evaluating the methodology and components of tests and optimizing performance in the laboratory. However, it is impossible to apply these activities to many commercial kits that use "black-box" methodology, i.e., those that use complex, non-transparent, or proprietary algorithms to determine a result. Test results that could potentially cause

harm to patients if incorrect and do not lend themselves to evaluation by the laboratory physicians and the patient's treating physician are most concerning to the AMA and are the type of test that belongs in the high-risk category. To the extent that many companion diagnostic tests are run using simple sequencing or variant identification methodology that is transparent and easily evaluated, the AMA believes it is inappropriate for the FDA to assign all companion diagnostic tests to the high-risk category. Aside from the absence of established risk criteria applied to each individual test's methodology as a basis for their placement in the high-risk category, the FDA appears to be casting aside the risk mitigation that occurs with a physician's (both ordering and laboratory) oversight and expertise in running the test and subsequently managing the patient.

Answer to Question #4: Safety and Effectiveness

4. The current pre-market review standards that apply to in vitro diagnostics use the same terminology of ***safety and effectiveness*** *that apply to all medical devices. Should the medical device concepts of safety and effectiveness apply to test kits and LDTs?*

The AMA does not support application of current medical device safety and effectiveness concepts to laboratory testing services because procedures and physician expertise are not devices. Furthermore, the FDA's application of statutory provisions intended for actual medical devices, drugs, and biologicals to manufactured commercial diagnostic kits is statutorily compulsory, but ill-suited to the consideration of validity (analytical and clinical) and risk/benefit relevant to diagnostics. Instead the Subcommittee should invite additional discussion on clinical and analytical validity as well as relevant risk/benefit models under both CLIA for laboratories where physician services are performed and FFDCA for commercial diagnostic kits, because laboratory developed testing services and commercial kits have relevant distinctions as outlined above.

Real Life Implications for Patients

One difficulty in applying the safe and effective standard devised for devices is that laboratory developed testing services are not devices. A suboptimal assay may function well and hence be "safe and effective" for what it does, but use of the information for a particular patient may result in suboptimal treatment. The current assay for KRAS testing of colon cancer is FDA approved (safe and effective), but it only detects mutations in codons 12 and 13. We now know that complete testing of colon cancers requires evaluation of multiple other codons in the KRAS gene (12, 13, 59, 61, 117, 146) and in the NRAS gene. Hence, in the recognized application of that assay, the limited test for KRAS would be of limited effectiveness and safety. The package insert for the drug panitumumab (Vectibix) states:

> Vectibix® is not indicated for the treatment of patients with KRAS-mutant mCRC or for whom KRAS mutation status is unknown. Vectibix® in combination with oxaliplatin-based chemotherapy is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown.
>
> RAS is defined as exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either KRAS or NRAS and hereon is referred to as "RAS."

So whether the limited KRAS assay is safe and effective depends on the intended treatment. There is no way for FDA to collect "adverse effects" of the clinical misapplication of this assay.

Answers to Question #5 and #6: Reforms to FDA Regulation of Commercial Testing Kits

5. Are there areas where the balance between pre-market review versus post-market controls should be reconsidered? How can post market processes be used to reduce barriers to patient access to new diagnostic tests?

6. A number of stakeholders have expressed concerns about uncertainty as to when a supplemental premarket submission is required for a modification. When should they be required prior to implementing modifications? Should the requirements for submission of a supplemental clearance or approval differ between LDTs and distributed test kits?

These two sets of questions underscore why comprehensive reform is required of current FDA regulation of commercial test kits and why expansion of FDA oversight to laboratory developed testing services would harm patients and undermine the practice of medicine across the country. Manufacturers have laid out a compelling case that the FDA's current approach lacks an appropriate balance between pre-market review versus post-market controls. If this has not been a large enough albatross hampering commercialization efforts by manufacturers, the Agency's moving target exercise of discretion around when a supplemental premarket submission is required for a modification has hamstrung efforts to improve upon commercial kits that would accelerate the availability of enhanced test kits that improve upon the earlier version. Reforming FDA authority over commercial kits on both counts would level the respective positions of commercial kits and physician testing services while increasing options and protecting physician clinical decision-making. In short, only clinically meaningful performance modification should trigger a supplemental for commercial kits. **The CLIA model of oversight has served as the engine of innovation in this space and rapid application of validated clinical discovery to patient care; therefore, any modifications should involve enhancements to CLIA and clear prohibitions against the FDA regulation of physician services because a commercial version of the test has been modified.**

Answer to Question #8: Reduce Duplicative and Costly Government Regulation

8. The Section 1143 guidance documents raise important questions about the relationship between the FFDCA and the Clinical Laboratory Improvement Amendments (CLIA), administered by the Centers for Medicare & Medicaid Services (CMS). Is there overlap between the requirements of the guidance documents and CLIA? For instance, how do FDA's quality systems regulations compare with CLIA quality systems requirements? Are there areas of duplication where there would be efficiencies to having either CLIA or FDA regulate, rather than both?

We agree that the Subcommittee is asking the right questions, but the FDA's draft guidance does not provide sufficient detail to ascertain where CLIA requirements end and where the FDA requirements begin. Years ago, the FDA committed to issuing a clear statement of CLIA and FDA requirements when it issued proposed draft guidance on regulation of physician developed laboratory testing services. The AMA has asked the Agency for this information and months have passed without a response. **The AMA strongly urges this Subcommittee to consider the compelling need to avoid duplicative and confusing regulation and oversight by two federal agencies, a number of states, and accreditation bodies with deeming authority.** The FDA has proposed a framework for regulation of LDTs, but has

not clarified nor produced any documentation of coordination with CMS based on this new proposal. Furthermore, the FDA has been silent as to the role of the Center for Disease Control and Prevention vis-à-vis CLIA and the new FDA requirements. (CDC, in partnership with CMS and FDA, supports the CLIA program and clinical laboratory quality.) Just as Congress charged the FDA, the Federal Communications Commission, and the U.S. Department of Health & Human Services Office of the National Coordinator for Health Information Technology to jointly develop a proposed regulatory framework for digital health to avoid duplicative and burdensome regulation, **there is similarly an urgent need to, at a minimum, require CMS, the CDC and the FDA to engage major stakeholders in a transparent process and propose a framework that clearly and specifically identifies areas where the agencies will avoid contradictory, overlapping, and or/and ambiguous oversight parameters.**

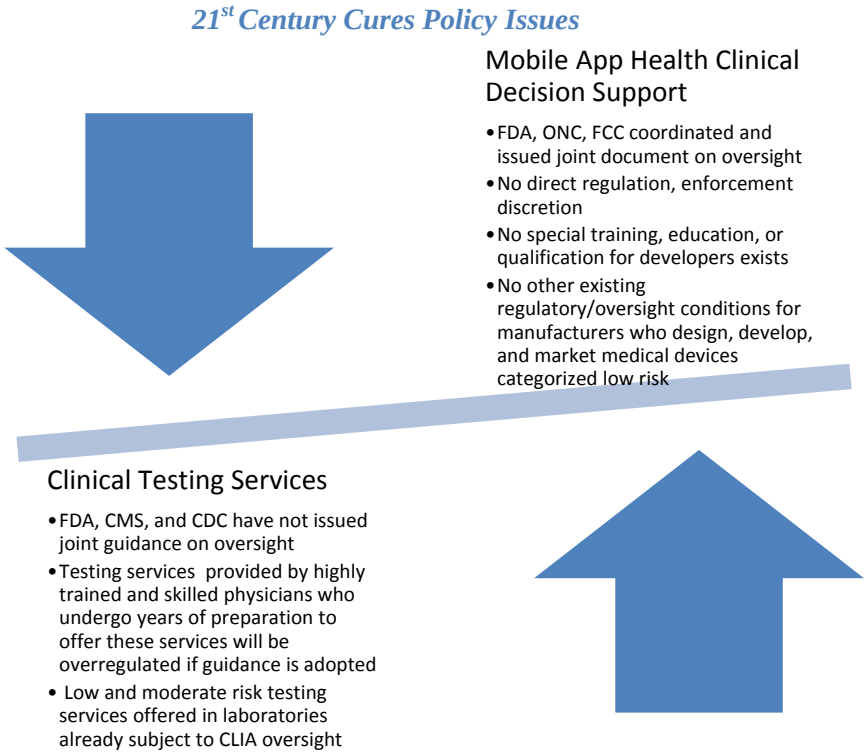


Figure 2. The FDA has taken markedly different regulatory approaches to certain clinical decision support mobile apps that are medical devices which will not be subject to direct regulation and may lack learned intermediaries for use as compared to physician laboratory developed testing services which are offered under regulated conditions by experienced and highly trained medical professionals.

Reportedly, there could be substantial overlap in the regulatory requirements under FDA medical device regulation and the applicable regulations under CLIA concerning quality system requirements, design controls, document controls, purchasing controls, production and process controls, acceptance activities, nonconforming products, corrective and preventative actions, and records. **We urge the Subcommittee to, at a minimum, direct the FDA to identify with CMS and the CDC the respective requirements and direct the FDA to defer to CLIA requirements where there is overlap.** Stakeholders must have an opportunity to comment on the proposal before it is finalized through notice and comment processes.

We are concerned that the Agency has already demonstrated that it lacks the bandwidth to expand oversight to laboratory developed testing services when it is unable to produce a guidance document promised years prior and which multiple stakeholders have requested in order to provide meaningful and informed comment on the FDA's proposed new and far reaching regulation.

Answer to Question #9: CLIA—The Proven Innovator

9. How should any regulatory system address diagnostic tests used for rare diseases or conditions, customized diagnostic tests and diagnostic tests needed for emergency or unmet needs (e.g. Ebola)?

We strongly urge the Subcommittee to build on and modernize the existing CLIA regulatory framework consistent with our recommendations because the current CLIA framework has a demonstrated track record of:

- Providing the necessary flexibilities to ensure patient access to testing services for rare diseases and conditions;
- Supporting customized testing services based on particularized patient need; and,
- Enhancing the capabilities of the country's safety net of highly skilled professionals and laboratories that can provide essential surge capacity and frontline access when there are outbreaks of infectious diseases and biothreats.

In sharp contrast, we are concerned that the FDA's regulation of commercial diagnostic kits—which for the most part has not been able to meet most of the foregoing needs—demonstrates unambiguously that the FDA framework of regulation is overly bureaucratic, expensive, and slow. The ability and capacity of the FDA to approve or clear commercial diagnostic kits has been paltry when compared with the breadth and range of testing services offered to patients under CLIA—with high rates of accuracy and rapid application of new and validated clinical knowledge. The Subcommittee should carefully consider that comprehensive reform of testing services should not expand the reach of a flawed FDA regulatory model that has created barriers to innovation, limited patient access to testing improvements, failed to provide any viable pathway for rare diseases and conditions, and utilizes a top-down, bureaucratic approach to outbreaks and potential biothreats. In addition to CLIA modernization, there is an urgent need to address and streamline the FDA's regulation of mass-produced commercial kits consistent with the AMA's recommendations.

The proposed application of the FDA regulatory framework to testing services for rare diseases, unmet needs, or emergency use—even with exemptions and carve-outs is unworkable and dangerous to individual patients and undermines overall public health by limiting and constraining the number of physicians and laboratories able to handle biothreats and infectious disease outbreaks.

Laboratory developed testing services are often the only option for those with suspected rare diseases. The commercial market for such tests is nearly non-existent, so laboratory-developed tests are a vital tool for patients and their physicians. As currently written, the FDA's proposed exemptions for rare diseases are inadequate in ensuring the continued availability of laboratory developed testing services; the definition pertains to rarely-performed tests, not rare diseases. For example, in one of the most stunning public health successes in history, every newborn in this country undergoes testing for dozens of conditions, which, if not identified within days of birth, can result in serious morbidity and mortality. Many of the conditions being tested are rare diseases, but that does not diminish the public health imperative for them to be identified and diagnosed in patients. However, since the number of newborn screening tests that are performed far exceeds the FDA's definition of rare disease (fewer than 4,000 persons tested each year), each one of the dozens of newborn screening tests may be subject to

burdensome requirements that could endanger their availability. The very definition of "rare" implies that many people will need to be tested in order to identify one, the equivalent of finding a needle in a haystack. For that reason, the cut-off of 4,000 persons per year being tested is utterly unreasonable. Because these tests often constitute a small volume of testing for most laboratories, FDA oversight would likely result in laboratories dropping the tests completely, leaving patients and physicians without an option for screening and diagnosis.

Similar to the lack of commercial availability for tests for rare diseases, many thousands of laboratory developed tests exist simply because commercially-developed kits do not exist, i.e., they fulfill "unmet needs." These laboratory developed testing services are for a broad range of conditions, and constitute the standard of care. For example, clinical guidelines recommend testing all newly-diagnosed colon cancers for Lynch syndrome, a hereditary colorectal cancer syndrome. Lynch syndrome testing includes assays for mismatch repair variants and microsatellite instability. This type of testing has been available as a laboratory developed testing service for more than 10 years and has been continually improved-upon as new research data emerges (e.g., including BRAF as part of the Lynch syndrome testing protocol). There are no FDA-approved tests for Lynch syndrome nor for microsatellite instability. Yet, the FDA's proposed exemption for this "unmet needs" test category ends as soon as a commercially-developed kit becomes available. When this happens, every laboratory that has developed a Lynch syndrome testing protocol would need to submit it to the FDA, likely as a pre-market approval application. The expense and burden required for such an activity would not be feasible for many laboratories, which would then decide not to continue Lynch syndrome testing. This would drive up costs, and would freeze further innovation and improvements to Lynch syndrome testing, leaving patients without access to cutting-edge care.

The nature of public health outbreaks demands that health systems respond rapidly. Laboratory medicine experts are able to fulfill this need by developing tests that accurately identify pathogens far more quickly than would be possible if FDA approval or clearance were required. For example, in April 2009 an unknown respiratory outbreak emerged in the U.S. and Mexico. During the first week of the outbreak, several dozen laboratories had already developed molecular assays that could identify the outbreak as being caused by influenza, and could distinguish the A and B strains. Several of the laboratories were further able to identify the H1N1 virus from other H1 viruses. Most results from these tests were available within 24 hours, speeding treatment of patients and decision-making by public health officials. FDA approval requirements would have severely crippled this response. FDA has the capability to issue Emergency Use Authorization, but these are temporary and therefore do not adequately or permanently address the problem.

Answer to Questions #10: Transition

10. Any new regulatory system will create transition challenges. How should existing products be handled? Should all current diagnostic tests be "grandfathered" into the marketplace? What transition process should be used for new product introductions?

The AMA proposal of modernizing CLIA oversight of laboratories where physicians provide testing services and reforming FDA regulation of commercial diagnostic kits would not create the disruption to patient clinical care and innovation that the FDA's current and proposed regulation have and will. Any congressional action to modify the existing oversight and regulation should grandfather in the vast majority of laboratory developed testing services as there is not adequate capacity outside of the AMA's proposal to account for the time and resources that will be required. In addition, Congress must consider that Medicare's reduction in coverage and reimbursement in the context of testing services will coincide with increased oversight and regulatory obligations. We strongly urge the Subcommittee to consider the

interplay between these dynamics for patient access to existing testing services as well as future innovation.

Answer to Question #11: Incentives

11. What incentives can be put in place to encourage the development of new, more accurate or more efficient diagnostic tests?

There are two major barriers to the development of new, more accurate, and efficient clinical testing: (1) current FDA regulation of commercial diagnostic kits and proposed regulation of laboratory developed testing services; and (2) draconian federal health care coverage policies. Simply stated, incentives are not created by limiting patient access through overregulation and coverage policies that deny access to demonstrably beneficial testing services. These government actions are adversely impacting the ability of patients to obtain medical care and exerting pressure on physicians who have lead the innovation to accelerate 21st Century Cures and related testing.

FDA Regulation Stymies 20th and 21st Century Cures and Testing. Manufacturers face commercialization challenges largely because of the burdensome, opaque, and lengthy FDA clearance and approval process. A recently issued independent analysis of the FDA's 510(k) review times belies the FDA's published statistics on the topic. In a study by the Medical Device and Diagnostic Industry (MDDI), and soon to be published in a 2015 MDDI periodical, the authors analyzed 510(k) review time data from FDA's publicly available database. The highlighted conclusions include the following:

- Use of the third-party review program has significantly declined, while the review times for 510(k)s have increased.
- There is no review-time advantage to submitting an Abbreviated 510(k) compared to a Traditional 510(k).
- Even those devices most frequently reviewed by FDA still saw an increase in their overall review times between 2008 and 2012.

The foregoing data analysis is only half the story. The agency's poor performance on review times for commercial diagnostic kits includes:

- Commercial diagnostic kit 510(k)s take significantly longer to review than 510(k)s for other types of devices.
- Between 2008 and 2012, the average review time for an IVD 510(k) was 183 days compared to a non-IVD 510(k) which was 127 days.

As noted by the authors of the article, the above findings are of particular importance given the FDA's proposed plan to regulate laboratory developed testing services. Reportedly, the same FDA staff reviewing commercial diagnostic kits will review laboratory developed testing services. It is highly improbable given budget forecasts that the FDA will have significantly more capacity to rapidly review and approve new tests. Understandably, the authors report that manufacturers have expressed concerns that FDA review of commercial kits will be further slowed once it begins regulation of physician laboratory developed services.

Real Life Implications for Patients

> I am a laboratory physician in a community teaching hospital. A few months ago a patient in his 20s presented symptoms of ureteral obstruction. A ureteral mass was surgically removed and diagnosed as an adenocarcinoma most consistent

with lung origin. Subsequent evaluation identified multiple lung nodules, with metastases to the mediastinum and abdomen, and pleural and pericardial malignant effusions (Stage IV). His course was complicated by cardiac tamponade due to the malignant pericardial effusion which was relieved by pericardiocentesis.

Biomarker evaluation of his tumor showed it to be negative for KRAS codon 12 and 13 mutations and negative for EGFR exon 19 and exon 21 mutations. Evaluation for the EML4-ALK translocation by fluorescence in situ hybridization (FISH) was negative, but a laboratory developed FISH assay was positive for the ROS-1 translocation, indicating that the tumor would likely respond to treatment with the targeted tyrosine kinase inhibitor crizotinib.

An initial request for coverage from his private insurer for crizotinib therapy was denied because neither the ALK nor ROS translocations had been documented at the time of the request. Once reported, the patient was started on crizotinib therapy. His oncologist reports that "after about three weeks on crizotinib, he began to feel better overall with less pain and improved ability to function. Based on the New England Journal of Medicine paper, I am hopeful that he will continue to improve clinically and his follow up imaging will confirm response." He is scheduled for follow-up evaluation shortly.

There is no FDA approved assay for detecting the ROS-1 translocation although it is rapidly becoming standard practice to test for it and to treat with crizotinib if the translocation is present, as evidenced by the insurer's coverage policy. My laboratory has been testing non-small cell lung cancer for the ROS-1 translocation for over a year and, more recently at the request of our oncologists, the laboratory now tests all non-small cell lung cancers for ALK and ROS-1 translocations.

The rate of clinical discovery has increased over time, largely as a result of the flexibility of the CLIA oversight model and increased computing capacity, CLIA allows for the rapid adoption of validated clinical discovery into medical practice. The FDA has consistently demonstrated it is not capable of keeping pace. There would be real consequences for the above twenty year old patient with adenocarcinoma if he had to wait for FDA clearance or approval.

The Agency has proposed a carve-out for “unmet needs” testing services, presumably like those testing services discussed above, until the FDA approves a commercial kit under the FDA proposed regulation. The testing service then becomes a “high risk” test for which pre-market approval must be pursued. This demonstrates that the Agency’s characterization of “risk” is a fiction and not rooted in actual risk. These are testing services used for the same purpose, performed with the same care and diligence and conditions in a CLIA certified laboratory. Why do the consequences amplify once a FDA approved or cleared commercial diagnostic kit exists? The physicians who are uniformly concerned about patient care and safety are the skilled medical professionals who make the effort to develop and validate laboratory developed testing services for patient care, and who have the patients' best interest in mind from day one. Secondly, the mere prospect of having to pursue FDA pre-market approval would deter most laboratories from developing this as an interim “unmet need” laboratory developed testing services. This test would not be as readily available, if at all, for this patient in the kind of world envisaged by FDA.

Medicare Coverage Policies: Hostile to 20th and 21st Century Cures and Testing Services. At the same time that Congress has actively discussed incentives to increase access to innovative testing options through changes to the regulatory pathway, the Medicare program, a pace setter for coverage among both

private and public payers, has implemented coverage decisions contrary to the weight of clinical evidence and clinical expertise of nationally recognized subject matter experts. The experts who have expressed opposition to these coverage policies hail from flagship academic medical centers, community laboratories, and leading reference laboratories. **These coverage decisions have constrained patient access to current testing and 21st Century cures.**

The College of American Pathologists, the American College of Medical Genetics and Genomics, and Association for Molecular Pathology have submitted detailed comments, peer-reviewed evidence and clinical practice guidelines to a key Medicare contractor that has issued coverage denials for a range of genetic clinical tests. To be clear, the coverage denials cover a broad number of previously covered genetic tests that represent the standard of care. These tests end the often lengthy and expensive diagnostic journey and result in patients obtaining life-saving treatments. These denials by the Medicare program create significant barriers to existing testing services, but also hamper the next generation of testing services (which are typically the necessary prerequisite to identification of viable commercial diagnostic kits). The Subcommittee should consider carefully scrutinizing the current Medicare coverage activities that are a real threat to appropriate patient medical care and the future of innovation.

Real Life Implications for Patients

> We [the Wilson's Disease Association (WDA) . . .] received a communication from one of our members that a Medicare contractor, Palmetto GBA, has determined that gene testing for the diagnosis of Wilson Disease is not a covered Medicare benefit, stating:
>
> > ATP7B gene mutations have been primarily associated with Wilson Disease, a disorder of copper metabolism. However, serology remains the gold standard for testing and treating the signs and symptoms of this condition. At present the literature does not support that ATP7B gene testing changes physician treatment or improves patient outcomes. Therefore, Palmetto GBA has determined ATP7B gene testing is a statutorily excluded service and panels of tests that include the ATP7B gene.[1]
>
> Palmetto is mistaken in its assertion that the literature does not support gene testing and that such gene testing will not change physician treatment or improve patient outcomes [for Wilson disease]. In fact, the peer reviewed clinical literature is clear, and well-established practice guidelines include gene testing: "[d]iagnosis of Wilson disease cannot be made by a single test alone and a combination of tests is always needed." Weiss KH. (2013) Wilson Disease, GeneReviews. Furthermore, […] the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines states: "[m]utation analysis by whole-gene sequencing is possible and should be performed on individuals in whom the diagnosis is difficult to establish by clinical and biochemical testing." In order to correctly treat individuals suspected of having Wilson disease, a diagnosis must be made. The notion that accurate diagnosis will not promote improved patient outcomes flies in the face of basic common sense as well as documented clinical evidence. The member who flagged this issue for WDA had

[1] Per Palmetto's website: Statutory Exclusion [Medicare] covers diagnostic testing "except for items and services that are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member,…".

> a parent who was/is a Medicare beneficiary who had a host of symptoms that suggested Wilson Disease, but for whom all other tests were not conclusive. (Contrary to Palmetto's assertions, the foregoing is not an uncommon occurrence.) This Medicare beneficiary underwent a significant diagnostic journey with multiple hospitalizations and visits to a large number of specialists. It was not until she underwent genetic testing that it was established she had Wilson Disease. This Medicare beneficiary's costly and deleterious diagnostic journey ended and she began to receive treatment.

The foregoing excerpt from a patient group to Medicare is an accurate characterization of the overwhelming medical literature and clinical expertise supporting continued access and coverage of genetic testing for suspected Wilson Disease (WD) when conventional testing is inconclusive. About 10 U.S. laboratories have medical professionals able to offer DNA sequencing analysis of the ATP7B gene, which causes WD. At least one laboratory has offered this service for nearly a decade. This test is an important tool in the WD diagnostic armamentarium as the more traditional testing procedures are all prone to inconclusive results. Furthermore, another option, a liver biopsy is expensive and often an unnecessarily invasive procedures for medically compromised patients as compared to genetic testing. The proper diagnosis of WD has very effective treatment options for most patients. When diagnosed early, patients have treatment options that will allow them to live long and productive lives. **If left undiagnosed/misdiagnosed these patients will suffer extreme morbidity, physically and mentally, ultimately leading to death.** Unfortunately, if the diagnosis is made late, treatment often at this stage cannot reverse all symptoms, especially psychological damage.

Despite all of the foregoing, Medicare, as with a large number of other genetic tests with equally compelling clinical evidence to support coverage, has left unchecked the coverage decisions of key contractors that are not supported by the weight of clinical evidence and the recommendations of the leading medical authorities. The negative impact of these coverage decisions undermines any efforts to innovate as the evidence bar moves in a capricious manner and contrary to patient interests. CMS coverage policies coupled with the FDA's overregulation of commercial kits and proposal to expand to laboratory developed testing services have begun to turn back the clock of medical innovation, patient access to life saving testing services, and the promise of widespread access touted when the Human Genome Project mapped the first reference genome. **A critical juncture has been reached and there is an urgent and immediate need that the Health Subcommittee clears the barriers that two overreaching federal agencies have erected to personalized medicine and 21st Century Cures.**

Concluding Comments

The Subcommittee is considering issues that have real consequences for whether patients are able to obtain often life-saving clinical testing services. The rate of discovery and innovation has been fueled by physician laboratory medical practice. The real question is whether heavy-handed government actions will obstruct continued progress in 21st Century medicine. We strongly urge the Subcommittee to move forward legislation that will rescind FDA's proposed regulation of laboratory developed testing services while modernizing CLIA and reforming FDA oversight of commercial kits. We further urge the Subcommittee to consider the negative impact of coverage decisions by federal health care programs on current patient access and future innovation.